BOSTON BIOMEDICAL
Sumitomo Dainippon Pharma Global Oncology

Protocol CanStem43L

A Phase III Randomized, Open-Label Clinical Trial of BBI-608 plus Weekly Paclitaxel versus Weekly Paclitaxel Alone in Patients with Advanced, Previously Treated, Non-Squamous Non-Small Cell Lung

Statistical Analysis Plan (SAP)

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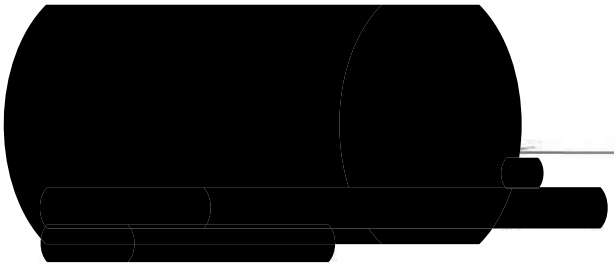
APPROVALS



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Contents

1. VERSION HISTORY

This is the first version of statistical analysis plan, based on the study protocol dated June 12rd, 2016 [1] and CanStem43L Investigator Letter on terminating the trial dated June 14, 2017 [2].

2. INTRODUCTION

2.1. Study Design

This is an international, multi-center, prospective, randomized, open-label Phase III clinical trial of BBI-608 plus weekly paclitaxel versus weekly paclitaxel alone in adult patients with advanced non-squamous NSCLC who have been previously treated with a platinum-based chemotherapy regimen in the metastatic setting, have received additional therapies, and for whom weekly paclitaxel is an acceptable treatment option.

Patients will be randomized 1:1 to receive treatment with either BBI-608 plus weekly paclitaxel or weekly paclitaxel alone. Randomization will be stratified by geography (North America/Western Europe/Australasia vs. Japan/Korea vs. Rest of World), previous targeted therapy for a known driver genetic mutation or rearrangement (yes vs. no), ECOG performance status (0 vs. 1), and whether the patient received prior treatment with an immune checkpoint inhibitor (yes vs. no).

The study will proceed in 28-day cycles that may be continued until the investigator determines that the patient is no longer potentially benefiting from therapy due to disease progression, unacceptable adverse events, or another discontinuation criterion. All patients will receive weekly paclitaxel on days 1, 8, and 15 of each study cycle, and patients randomized to Arm 1 will receive BBI-608 orally, twice daily, continuously. BBI-608 administration will begin 2 days prior to the first scheduled dose of paclitaxel for patients randomized to Arm 1.

The first objective (radiologic) disease evaluation will occur at 8 weeks (56 days) from the date of randomization, and will continue every 12 weeks thereafter until radiologic disease progression is confirmed by RECIST 1.1 criteria.

Two interim analyses for overall survival (OS) are planned: one when 50% of study events have occurred and a second when 80% of study events have occurred.

2.2. Study Population

The trial will enroll patients with histologically or cytologically confirmed recurrent, locally advanced, or metastatic non-squamous non-small cell lung cancer who have failed platinum-based therapy and an immune checkpoint inhibitor, if a candidate, and for whom weekly paclitaxel is a reasonable treatment option. Patients with tumors that harbor an EGFR or ALK/ROS1 genetic aberration must have received appropriately targeted therapy.

Patients must have received platinum-based therapy in the metastatic setting. Patients may be eligible if they progress or have disease recurrence within 6 months of receiving either perioperative chemotherapy or definitive chemo-radiation with platinum-based therapy, provided the regimen did not contain a taxane. Patients who have had prior treatment with a taxane in the metastatic setting are excluded. Prior treatment with a taxane is permitted only in the adjuvant, neo-adjuvant, or chemoradiation setting. Patients who receive perioperative treatment or definitive chemoradiation and who have disease recurrance or progression outside of 6 months will require a platinum-based regimen in the metastatic setting in order to be eligible.

Patients who are candidates for immunotherapy must have received treatment with pembrolizumab, nivolumab, or an alternate agent targeting the programmed cell death 1 receptor (PD-1) or programmed cell death ligand 1 (PD-L1), provided the agent has received approval as an "Investigational New Drug" (IND).

Prior treatment with other approved agents such as pemetrexed or erlotinib is permitted.

Patients with squamous type tumor histology are excluded. Patients with mixed histologic morphology are eligible provided the pathologist confirms that the tumor is predominantly non-squamous or predominantly adenocarcinoma. Patients with poorly differentiated tumors or with tumors lacking sufficient histologic morphology to assess sub-type may be eligible provided immunohistochemical (IHC) analyses are positive for the adenocarcinoma marker TTF-1 or Napsin A; and, in addition, are negative for the squamous cell marker p63 or p40.

Additional inclusion criteria include: age $\geq$ 18 years, ECOG performance status 0 or 1, and adequate end-organ function.

2.3. Study Objectives

2.3.1. Primary Objective

- To compare overall survival in patients with previously treated metastatic non-squamous non-small cell lung cancer (non-squamous NSCLC) who are randomized to receive treatment with BBI-608 plus weekly paclitaxel versus weekly paclitaxel alone.

2.3.2. Secondary Objectives

- To compare OS in patients with previously treated metastatic non-squamous NSCLC who are biomarker positive and who are randomized to receive treatment with BBI-608 plus weekly paclitaxel versus weekly paclitaxel alone.
- To compare progression free survival (PFS, defined as the time from randomization until disease progression per RECIST 1.1 or death) in patients with non-squamous NSCLC who are randomized to receive treatment with BBI-608 plus weekly paclitaxel versus weekly paclitaxel alone.

- To compare PFS in patients with non-squamous NSCLC who are biomarker positive and who are randomized to receive treatment with BBI-608 plus weekly paclitaxel versus weekly paclitaxel alone.
- To compare the disease control rate (DCR, defined as the proportion with complete response, partial response, or stable disease per RECIST 1.1) and overall response rate (ORR, defined as the proportion with either complete response or partial response per RECIST 1.1) observed in patients with non-squamous NSCLC randomized to receive treatment with BBI-608 plus weekly paclitaxel versus weekly paclitaxel alone.
- To compare the DCR and ORR observed in patients with non-squamous NSCLC who are biomarker positive and who are randomized to receive treatment with BBI-608 plus weekly paclitaxel versus weekly paclitaxel alone.
- To compare Quality of Life (QoL) as measured using the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ-C30), in patients with advanced non-squamous NSCLC randomized to receive BBI-608 plus weekly paclitaxel versus weekly paclitaxel alone.
- To evaluate the safety profile of BBI-608 administered with weekly paclitaxel versus that of weekly paclitaxel alone according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) in patients with advanced non-squamous NSCLC randomized on study.

2.3.3. Exploratory Objectives

- To evaluate OS, PFS, DCR, and ORR in randomized patients as treated.
- To evaluate OS, PFS, DCR, and ORR in randomized patients who are without major violations of the protocol.
- To evaluate the influence of demographic and clinical factors such as age, gender, histology, prior treatments and others on study outcomes.
- To perform sparse pharmacokinetic sampling and to evaluate study endpoints according to measures of pharmacokinetic exposure. Additionally, clinical factors potentially affecting exposure may be evaluated.
- To investigate predictive and pharmacodynamic biomarkers of BBI-608 administered in combination with weekly paclitaxel in patients with advanced non-squamous NSCLC.

3. ENDPOINTS

3.1. Primary Endpoints

- Overall Survival

3.2. Secondary Endpoints

- Overall Survival in the predefined biomarker-positive sub-population[¥]
- Progression Free Survival in the ITT study population
- Progression Free Survival in the predefined biomarker-positive sub-population[¥]
- Disease Control Rate & Objective Response Rate in the ITT study population
- Disease Control Rate & Objective Response Rate in the predefined biomarker-positive sub-population[¥]
- Quality of Life
- Safety Profile

[¥]The biomarker-positive sub-population is defined as those patients positive for phosphorylated STAT3 (p-STAT3) based on immunohistochemical (IHC) staining of Formalin-Fixed, Paraffin-Embedded (FFPE) tumor tissue.

3.3. Exploratory Endpoints

- OS, PFS, DCR, and ORR in randomized patients as treated.
- OS, PFS, DCR, and ORR in randomized patients who are without major violations of the protocol.
- Co-factors (demographic and clinical factors such as age, gender, histology, prior treatments) influencing study outcomes.
- Clinical factors affecting exposure utilizing sparse pharmacokinetic sampling.
- Prediction of pharmacodynamic biomarkers of BBI-608 administered in combination with weekly paclitaxel in patients with advanced non-squamous NSCLC.

4. SAMPLE SIZE, POWER AND INTERIM ANALYSIS

The study is designed to have a power of 90% and a two-sided alpha of 5% to detect a 22% reduction in the continuous risk of death in the Intention to Treat (ITT) study population (HR 0.78, which corresponds to an increase in median survival from 8.2 months to 10.5 months). A total of 694 death events are required, which would be observed by randomizing 870 patients over 24 months, with 12 months minimum follow-up for each patient. The sample size calculation assumes a drop-out rate of up to 5% for the entire study.

There are two interim analyses planned for overall survival, one at 50% of events and another at 80% of events. Each of these analyses will use a log-rank test to compare treatment to controls and will test survival for the following:

H0: BBI-608 + weekly paclitaxel $\leq$ weekly paclitaxel

versus

H1: BBI-608 + weekly paclitaxel > weekly paclitaxel

A generalization of the Lan-DeMets error spending function approach will be used to define superiority by using an O'Brien-Fleming stopping boundary to reject H0, controlling for a two-sided alpha of 5% at the end of the study. The number of events in the database will determine the nominal critical point and the p-value for declaring superiority.

For the first interim analysis, if exactly 347 events (50% of 694) were in the locked database, the nominal critical point for rejecting H0 would be 2.963. That is, H0 would be rejected and superiority of BBI-608 declared at this interim analysis if the difference in median survival favors a treatment effect and the p-value from the stratified log-rank test is $\leq$ 0.003. If the trial does not stop at this analysis, it will continue to the second interim analysis.

For the second interim analysis, if exactly 556 events (80% of 694) were in the locked database, the nominal critical point for rejecting H0 would be 2.266. That is, H0 would be rejected and superiority of BBI-608 declared at this interim analysis if the difference in median survival favors a treatment effect and the p-value from the stratified log-rank test is $\leq$ 0.023. Should the trial not stop for efficacy at this point in the analysis, it will continue to the final analysis.

The final analysis will occur when at least 694 events are observed. With exactly 694 events, the nominal critical value for rejecting H0 at the final analysis would be 2.028. That is, the superiority of BBI-608 would be declared at the final analysis if the difference in median survival favors a treatment effect and the p-value from the stratified log-rank test is $\leq$ 0.043.

5. DECISION OF TERMINATING THE TRIAL EARLY

On June 12, 2017, BBI issued an letter to inform the CanStem43L investigators that the study CanStem43L will be terminated.

Per letter: "After an in-depth review and much deliberation, this letter is written to notify you that the CanStem43L clinical trial will be discontinued. Effective immediately, further ethical or scientific committee reviews are not required and study close-out procedures can begin. This decision was not made lightly and follows extensive discussions with multiple internal and external stakeholders. The CanStem43L trial is being stopped for corporate reasons that are explained below, and there have been no abnormal or unexpected safety findings during the study.

The standard of care for patients with non-small cell lung cancer (NSCLC) is evolving rapidly. In this context, there was a high risk that the end of the trial could result in a potential benefit proven in a setting no longer relevant to clinical care. Though there is a risk of irrelevancy in any clinical trial, the recent developments for patients with metastatic NSCLC, and the wide array of on-going clinical trials, increased that risk substantially for CanStem43L. This difficult decision to discontinue CanStem43L allows for important resources to be focused on achieving the goal of turning napabucasin and other innovative compounds into therapeutic realities for cancer patients everywhere."

There were only four patients enrolled into the study by the time the decision was made to terminate the trial.

6. STATISTICAL ANALYSIS

There are only four patients enrolled into the study. Due to limited actual sample size, there will not be statistical inference or summary for data by treatment and/or overall. Only the listings of individual demographic, baseline characteristics and safety data will be reported. Such listings may include the following:

- Randomization, treatment, and strata
- Demographic and baseline characteristics
- Baseline disease characteristics
- Medical history
- Prior cancer surgery
- Prior hormone/biologics/chemotherapy/other Therapy
- Treatment discontinuation, study withdrawal and corresponding reasons
- Drug administration
- Adverse events
- Serious adverse events
- Deaths
- Laboratory data

7. REFERENCES

1. Protocol CanStem43L, A Phase III Randomized, Open-Label Clinical Trial of BBI-608 plus Weekly Paclitaxel versus Weekly Paclitaxel Alone in Patients with Advanced, Previously Treated, Non-Squamous Non-Small Cell Lung, June 12rd, 2016

2. BBI letter to CanStem43L Investigators on terminating Study CanStem43L, June 14, 2017